Poster Abstracts

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IL-10 Cooperates With TNFα to Activate Human Immunodeficiency Virus Type 1 From Latently and Acutely Infected Cells of Monocyte-Macrophage Lineage.

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Infection with human immunodeficiency virus type-1 (HIV-1) leads to the progressive loss of $CD4^+$ T cells followed by an increase in susceptibility to opportunistic infections and lymphomas eventually resulting in acquired immunodeficiency syndrome (AIDS). Interleukin-10 (IL-10) is an anti-inflammatory cytokine that is capable of inhibiting T lymphocyte proliferation and cytokine production. IL-10 is elevated in HIV-1 infected individuals and has been implicated in disease progression. It has been speculated that synthesis of IL-10 may lead to the suppression of T cells involved in cell-mediated immunity to the virus. Thus, it is important to determine whether IL-10 directly affects the expression of HIV-1 in infected cells and/or in modulating the inducibility of the virus in response to other cytokines. In this study, we investigated the effects of IL-10 on the activation of HIV-1 from infected monocytes and macrophages. Although IL-10 alone did not induce HIV-1 replication, in the presence of tumor necrosis factor α (TNFα), IL-10 markedly enhanced virion production from a chronically infected promonocytic cell line (U1) and in acutely infected monocyte-derived macrophages. Neutralizing monoclonal antibodies to IL-10 and TNFα indicated that both cytokines were essential for the induction and the two cytokines cooperated to generate a synergistic increase in virion production. The effects of the two cytokines were not functionally equivalent since pretreatment with TNFα attenuated the cytokine cooperativity, while pretreatment with IL-10 potentiated their cooperativity by further augmenting viral replication, suggesting that IL-10 may function to prime the TNFα response. Northern blot analysis as well as antibody blocking and cytokine secretion studies indicated that the induction of either endogenous TNFα or IL-10 was not involved in the cooperativity, nor was an upregulation of TNFα receptors. In combination with TNFα, IL-10 stimulated AP-1 and NF-κB binding activities, increased HIV-1 mRNA expression, and enhanced long terminal repeat-directed transcription through activation of the NF-κB binding sites, suggesting that the IL-10 effect occurs at least in part at the transcriptional level. Thus, in addition to down-regulating the cellular immune response to HIV-1, IL-10 may also play a role in TNFα-mediated activation of HIV-1 replication in monocytes and macrophages.

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